crest with reduced numbers of neural crest derived cells seen in the facial primordia. Using positional mapping we identified Pak1ip1 as the mutated gene in mray mice. Through previous work in yeast Pak1ip1 has been characterized as a negative regulator of Pak1 activity linking it to processes of cytoskeletal rearrangement, cell polarity and morphogenetic movements. Expression analysis shows that Pak1ip1 and Pak1 are widely expressed during embryonic development, underlining the idea that they are fundamental regulators of cellular morphology during development.

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Program/Abstract # 378
An ENU screen reveals novel genes in mammalian forebrain development
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The forebrain is the largest portion of the human brain and is responsible for many higher order cognitive functions including reasoning and memory. To identify genes required for mammalian forebrain development, we have conducted an ENU mutagenesis screen in the mouse. Using this unbiased, forward genetic approach, we have ascertained seven mutations affecting CNS development and have thus far identified four by positional cloning. The most remarkable phenotype uncovered to date is the *rudolph* mutation with severe developmental defects in both the CNS and appendicular skeleton (smaller long bones). The organization of the neocortex is profoundly disrupted and contains clustered cell bodies, which appear to be neurogenic foci. The causal gene is known to play a role in cholesterol biosynthesis, which is notable given the recent implication of a role for oxysterols in mediating intracellular components of Hedgehog signaling. We see decreased induction of known Sonic hedgehog (*Shh*) target genes in the cortex, retina and skeleton. In vitro, this mutation results in decreased cellular response to Shh, revealing a requirement for embryonic cholesterol metabolism in both CNS development and normal Shh signaling. Other mutations in our screen show phenotypes such as cortical hypocellularity, hydrocephaly, anterior encephalocele, and craniorachischisis. Thus, we have demonstrated the utility of a forward genetic approach in studying neurodevelopment. We will also describe our efforts to enrich our screen for mutations affecting forebrain development.

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Program/Abstract # 379
Sprouty gene function is required for normal sensory cranial nerve morphology
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The sensory cranial ganglia are derived from late migrating neural crest cells and regions of ectodermal thickening called placodes. Fibroblast growth factors (Fgfs) have been implicated in olfactory, epibranchial and otic placode development, as well as neural crest migration. The Sprouty (*Spry*) gene family encodes feedback antagonists of Fgf signalling. Between E8.5 and E9.5 *Spry1* and *2* are transiently expressed in the region of the developing epibranchial placodes and late migrating neural crest cells. Embryos lacking both *Spry1* and *Spry2* exhibit abnormal morphology in the proximal and/or distal regions of the cranial nerves V, VII/VIII, IX and X. Aberrant *Sox 10* expression at E9E9.5 implies that Spry is required for the development of late migrating neural crest cells. However, the sensory cranial ganglia in the neural crest-specific conditional *Spry1;2* double knockout (*Wnt1cre; Spry1*$^{flox/-}$;*2*$^{flox/-}$) are normal, suggesting that *Spry* expression within neural crest cells is not required for normal development. Alternatively Spry may have a role in placodal formation and differentiation as the expression of placodal and early neuronal markers is altered at E9.5 in *Spry1; 2* double knockouts. Together this data indicates that *Spry* gene function is required for the development of the sensory cranial ganglia.

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Program/Abstract # 380
Morphogenic defects of the head and spinal cord associated with high levels of folinic acid in ICR mice during mid-embryogenesis (E11E14)
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Folate supplementation has been used to prevent neural tube defects (NTDs) during pregnancy for many years. NTD and NTD related defects span a wide range from minor spinal malformations through occulta (mild), to anencephaly (severe). Although folate appears to prevent most NTDs some still occur whether from genetic abnormalities or for environmental factors. For our research group two important questions are is there one level of folate that should be sustained during pregnancy or should the recommended folate levels be stage specific and whether excess levels folate can alter embryonic development? Timed pregnant ICR mice were treated on the evening of E11 with sterile saline, 1 X FA (12mg/kg folinic acid) or 4 X FA (48mg/kg folinic acid). On days E12 and E13 they were treated in the morning with either sterile or 20mg/kg Methotrexate (MTX) and 1 X FA or 4 X FA and in the evening with either sterile or 1 X FA or 4 X FA resulting in 4 experimental groups. We observed spinal deformities in mice that received higher dose of folinic acid. Defects observed included improper neural tube closure at the cervical and/or lumbar region of the spinal cord, improper fusion of the spine resulting in major defects. Defects were also noted in the fore and hindbrain. This leads us back to the key question Do you need the same level of folate at all times during pregnancy? Or should folate levels be stage specific?

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Program/Abstract # 381
Characterization of the ontogeny of the circadian clock in the embryonic eye of *Xenopus laevis*
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Circadian oscillators are endogenous time-keeping mechanisms that drive twenty four hour rhythmic changes in gene expression, metabolism, hormone levels, and physical activity. We have characterized the developmental expression of genes known to regulate circadian rhythms. Core circadian oscillator genes (*xPeriod1* and *2*, *xBmal1*, *xClock*, *xCryptochrome1*, and *2*) as well as genes acted upon by the oscillator (outputs; *xNocturnin* and *xNAT*) are expressed in the developing nervous system and eye. These genes were differentially expressed in non-neural tissues such as the somites, heart, cement gland, and pronephros. The ontogeny of circadian rhythm in the embryonic eye was studied by isolating eyes at the appropriate developmental age every 4h in a 12hour lightdark cycle. *xBmal1*